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Full-length Article

Inflammatory dietary patterns and depressive symptoms in Italian older adults

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ABSTRACT

Background: Older adults are more susceptible to higher inflammatory levels and depression. Moreover, diet may influence inflammation as well as depression but no previous study examined whether inflammatory dietary patterns are related to depression in an older population.
To investigate the longitudinal association between inflammatory dietary patterns (using reduced rank regression (RRR)) and depressive symptoms in a population sample of Italian older adults.
Methods: We included 827 participants (aged ≥ 65 years) at baseline in 1998. Follow-up measurements were collected after 3, 6 and 9 years. We used RRR to identify inflammatory dietary patterns at baseline. The Centre for Epidemiologic Studies Depression (CES-D) scale was used to assess depressive symptoms by using continuous scores and depression by using a cut-off point (CES-D ≥ 20).
Results: We identified two inflammatory dietary patterns using different sets of response variables. Dietary pattern I was related to inflammatory markers C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor α and was characterized by high intakes of refined grains, sweet snacks, pasta and rice. After full adjustment for confounders, no longitudinal association was found when comparing extreme quartiles of this dietary pattern and depressive symptoms (Q1 vs Q4, model 4: B = 0.04, 95% CI: −0.06, 0.13) or depression (Q1 vs Q4, model 4: OR = 0.90, 95% CI: 0.55, 1.45). Dietary pattern II was related to inflammatory markers CRP, IL-18, IL-1β, IL-1 receptor antagonist and was characterized by high intakes of pasta, sugar-sweetened beverages, processed meat and chocolate and sweets. When comparing extreme quartiles, this dietary pattern was not longitudinally associated with depressive symptoms (Q1 vs Q4, model 4: B = −0.04, 95% CI: −0.13, 0.05) but an inverse association was found for depression (Q1 vs Q4, model 4: OR = 0.56, 95% CI: 0.40, 0.94).
Conclusion: Our study does not support the hypothesis that dietary patterns linked to inflammatory markers are associated with higher depressive symptoms and higher depression incidence. However, dietary intake in our population of older adults was quite homogeneous which makes it difficult to show clear associations.

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1. Introduction

Depression is a mental health disorder that is highly prevalent in older adults and is associated with reduced quality of life and increased morbidity and mortality rates (Charney et al., 2003; Blazer, 2003). An important predictor for depression in this specific age group is the number of chronic diseases, with inflammatory processes as a common link (Vink et al., 2008; Howren et al., 2009). Furthermore, there is a growing body of evidence that higher levels of the inflammatory biomarkers C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor α (TNF-α) and IL-1 are related to higher depressive symptoms (Howren et al., 2009; Goldsmith et al., 2016; Haapakoski et al., 2015; Hiles et al., 2012;

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Milaneschi et al., 2009). A suggested underlying mechanism for this link is that pro-inflammatory markers modulate the synthesis, release and re-uptake of mood-related neurotransmitters (e.g. serotonin and dopamine) (Sanchez-Villegas and Martinez-Gonzalez, 2013; Miller and Raison, 2016).

The origin of the mild pro-inflammatory state, that is typical in older persons, is still not clear but there is some evidence that inflammation is sustained in part by modifiable lifestyle factors, such as physical activity and diet (Luciano et al., 2012; Collard et al., 2015). Moreover, consuming an unhealthy dietary pattern, with high intakes of high-sugar and high-fat snacks, sugar-sweetened beverages, processed meat and fast foods, might increase the risk of depression (Akbaraly et al., 2009; Le Port et al., 2012; Jacka et al., 2017). Therefore, investigating the role of diet and depression and the influence of inflammation in older adults is needed. There is an increasing amount of evidence that inflammation is influenced by diet (Barbaresko et al., 2013; Minihane et al., 2015; Esmaillzadeh et al., 2007; Lopez-Garcia et al., 2004) but until now, few studies investigated the relationship between dietary patterns, inflammation and depressive symptoms in older adults, with contrasting results (Luciano et al., 2012; Milaneschi et al., 2011). Milaneschi et al. found that a Mediterranean diet can buffer the effect of depression on IL-6 inflammation levels in older Italian adults (Milaneschi et al., 2011), while a Scottish study did not find a moderating effect of a Mediterranean diet in the depressive symptoms-inflammation relationship (Luciano et al., 2012). Another study, performed in the same sample, investigated dietary patterns in relation to inflammation and observed that a Mediterranean diet was associated with lower fibrinogen levels, but not with lower CRP levels. In contrast, a "health aware" (low-fat) diet was associated with lower CRP levels (Corley et al., 2015). These previous studies support the hypothesis that a Mediterranean dietary pattern may prevent or downregulate inflammation. However, more recent studies suggest that inflammation is more likely to be influenced by 'unhealthy' Western-type dietary patterns (Barbaresko et al., 2013; Esmaillzadeh et al., 2007). Additionally, strong evidence for the link between unhealthy dietary patterns and inflammation has been offered by recent studies that have explored the inflammatory potential of dietary patterns in relation to depression by using the dietary inflammatory index (DII). These studies have consistently observed that a more pro-inflammatory dietary pattern was related to higher depressive symptoms (Shivappa et al., 2016; Sanchez-Villegas et al., 2015; Akbaraly et al., 2016; Lucas et al., 2014). All these recent studies on unhealthy dietary patterns were performed in middle-aged populations, while there are some suggestions in the literature that unhealthy Western-type dietary patterns are related to higher depressive symptoms in middle-aged adults (Akbaraly et al., 2009; Le Port et al., 2012; Jacka et al., 2017) but not in older adults (Chan et al., 2014; Gougeon et al., 2015).

In summary, older adults are more susceptible to higher inflammatory levels as well as depression (Organization, 2016; Panda et al., 2009; Krabbe et al., 2004). Diet may influence inflammation as well as depression, to our knowledge, no previous studies examined the influence of inflammatory dietary patterns on depression in an older population. Therefore, the objective of this study is to investigate the longitudinal association between inflammatory dietary patterns (using reduced rank regression (RRR)) and depressive symptoms in a population sample of older Italian adults. RRR allows us to empirically identify inflammatory dietary patterns by incorporating disease-specific inflammatory biomarkers as intermediate response variables in deriving these dietary patterns. We hypothesize to identify unhealthy dietary patterns that are highly associated to the included inflammatory biomarkers. Consequently, it is expected that higher consumption of these unhealthy dietary patterns are related to higher depressive symptoms and depression.

2. Methods

2.1. Subjects and study design

The InCHIANTI (Invecchiare in Chianti, aging in the Chianti area) study is an ongoing Italian population-based cohort study performed in two sites in Tuscany, Italy (Greve in Chianti and Bagno a Ripoli) among 1155 older adults (≥65 years). Baseline data collection took place from 1998 until 2000 and follow-up data were collected after 3, 6 and 9 years (from 2001 to 2003, 2004 to 2006 and 2007 to 2009, respectively). Participants conducted a home interview where data on lifestyle, diet and depression was collected. Consequently, a clinical examination was performed at the study location within 21 days after the home interview. More information about the study protocol can be found elsewhere (Ferrucci et al., 2000). The ethics committee of the Italian National Institute of Research and Care on Aging approved the study protocol and informed consent was obtained from all individual participants included.

2.2. Depressive symptoms assessment

Depressive symptoms were measured by using the Centre for Epidemiologic Studies Depression (CES-D) scale at baseline and after 3, 6 and 9 years and was completed by the participants during the home interview (Radloff, 1997). The CES-D is a 20-item self-report questionnaire with scores ranging from 0 to 60 points. In this study, we used continuous CES-D scores, hereafter referred to as "depressive symptoms" and CES-D scores as dichotomous outcome (CES-D ≥20), hereafter referred to as "depression". The cut-off point of CES-D scores ≥20 has been previously validated for identifying depression in older adults (Beekman et al., 1997) and an Italian population (Fava, 1983).

2.3. Laboratory procedures of inflammatory markers

During the clinical examination at baseline, blood samples were drawn in the morning after an overnight fast of almost 12 hours and after participants had been sedentary for at least 15 minutes. A 60-ml blood sample was drawn and delivered within two hours to the central laboratory that performed several tests of hematology and clinical chemistry and prepared the samples for the biological bank and were stored at −80 °C. The samples had never been previously thawed until 2003, when they were used to measure circulating levels of cytokines. Serum CRP was measured in duplicate with the Dade Behring (now Seimens) BNII nephelometer (Dade Behring Inc., Deerfield, IL, USA). Serum levels of Soluble IL-6, IL-1β, IL-1ra, TNF-α receptor II (kits from BIOSOURCE International, Camarillo, California) and IL-18 (kits from Quantikine HS, R&D Systems, Minneapolis, Minnesota) were measured by ELISA kits. The inter-assay coefficients of variation were as follows: 4.5% for IL-1ra, 5% for CRP and 7% for IL-6, TNF-α, IL-1β and IL-18.

2.4. Dietary pattern assessment at baseline

A country-specific validated food frequency questionnaire (FFQ) from the European Prospective Investigation into Cancer study was used to collect dietary data at baseline and contained 248 questions with 188 different food items (Riboli et al., 2002; Pala et al., 2003). The validation procedure for the FFQ has been described in more detail elsewhere (Pisani et al., 1997).

We used RRR to identify inflammatory dietary patterns at baseline. RRR identifies patterns in a set of food groups that explain the maximum variation in a number of response variables. These response variables can be nutrients or biomarkers that are hypothesized to be intermediates between the food groups and the outcome of interest (Weikert and Schulze, 2016; Hoffmann et al., 2004). A recent review stated that RRR can be used efficiently in nutritional epidemiology to identify dietary patterns associated with selected response variables that have known relations with a disease outcome of interest (Ferrucci et al., 2000). We performed RRR twice by incorporating two different sets of response variables. For the first dietary pattern we used the inflammatory biomarkers CRP (μg/mL), IL-6 (ng/mL) and TNF-α (pg/mL) as response variables because there is extensive evidence from the literature that these biomarkers are related to higher depressive symptoms (Haapakoski et al., 2015; Strawbridge et al., 2015). Additionally, a previous study identified inflammatory dietary patterns using RRR by incorporating the same response variables (CRP, IL-6, and TNF-α) in relation to depression (Lucas et al., 2014) and was validated afterwards by examining how well the identified dietary pattern predicted concentrations of IL-6, CRP and TNF-α in two independent samples (the Nurses' Health Study (n = 1002) and the Health Professionals Follow-up Study (n = 2632)) (Tabung et al., 2016).

For the second dietary pattern, we incorporated inflammatory biomarkers IL-1β (pg/mL), IL-1ra (pg/mL), CRP (μg/mL) and IL-18 (pg/mL) as response variables because these inflammatory biomarkers were indicated to be positively associated with incident depressive symptoms by a previous study in the InChianti study population (Milaneschi et al., 2009). Single food items from the FFQ were aggregated into 30 predefined food groups according to their nutritional composition and usual intake based on the Italian National Food Consumption Data (Table 1). Energy-adjusted food groups (using the residual method) were used as predictor variables in the RRR analyses as preliminary analyses revealed unequal distribution of energy intake across quartiles in the identified inflammatory dietary patterns. Continuous dietary pattern scores were divided into quartiles to get more insight into the trend of the association across quartiles, with higher quartiles indicating higher intake of the food groups that are characteristic for the identified dietary patterns. We used the first dietary pattern score of both RRR analyses for further analyses because this explained the highest amount of variation in food groups and response variables and the majority of the inflammatory biomarkers were highly correlated to the dietary patterns compared to the remaining dietary pattern scores. To get more insight into the identified dietary patterns, we investigated the median intake and interquartile range (IQR) of the most important food groups across quartiles of the identified dietary patterns. Hereby we could examine whether there is a difference in the actual intake of the food groups that strongly contributed to the dietary pattern scores of the inflammatory dietary patterns. The RRR method has been described in more detail elsewhere (Hoffmann et al., 2004).

Table 1
Food groups from the food frequency questionnaire for identification of dietary patterns according to their nutritional composition and usual intake.

	Food group	Food items
1	Red meat	Beef, veal, pork, horse, lamb
2	Processed meat	Processed meat, offals
3	Poultry	Chicken, turkey
4	Game	Rabbit, game
5	Fish	Fish
6	Shellfish	Crustaceans and molluscs
7	Eggs	Eggs
8	Butter	Margarine, other animal fat, butter, unclassified oil or fat
9	Vegetable oils	Other vegetable oils (except olive oil)
10	Olive oil	Olive oil
11	Dairy products	Milk, yoghurt, cheese
12	Fruit	Fruit
13	Nuts and seeds	Nuts and seeds
14	Other vegetables	Root vegetables, fruiting vegetables, cabbage, mushroom, mixed salad, stalk vegetables, onion and garlic
15	Leafy vegetables	Raw leafy vegetables, cooked leafy vegetables
16	Legumes	Legumes
17	Potatoes	Potatoes
18	Bread	Bread
19	Pasta	Pasta
20	Refined grains	Crisp bread and rusks, crackers and breadsticks, dry cake and biscuits
21	Rice	Rice
22	Wine	Wine
23	Other alcoholic beverages	Beer, cider, spirits
24	Coffee and tea	Coffee, tea
25	Sugar sweetened beverages	Fruit- and vegetable juices, soft beverages, isotonic beverages
26	Chocolate and sweets	Chocolate confections, non-chocolate confections
27	Sweet snacks	Ice cream, cake, pies, pudding, pastry
28	Added sugar	Sugar, honey, jam
29	Sauces	Sauces, mayonnaise and similar sauces, other sauces
30	Soups	Soups, bouillon

2.5. Covariates

Models were adjusted for several confounding factors assessed at baseline which were determined a priori based on previous research: baseline depressive symptoms (as continuous scores and as cut-off point (CES-D ≥20)), age (in years), sex, education (in years), marital status (never married, married, widowed or divorced), instrumental activities of daily living scale (IADL) (scores: 0–8), smoking status (never smoker, former smoker, current smoker), waist circumference (cm), physical activity level over the last year [(inactive (hardly any physical activity and mostly sitting or some walking), light (light exercise 2–4 h/wk), and moderate to intense (light >4 h/wk, moderate >3 h/wk or intense walks many times/wk)], use of antidepressants (yes or no), use of nonsteroidal anti-inflammatory drugs (yes or no), diabetes mellitus type 2 (blood glucose >126 mg/dl) (yes or no) and cardiovascular disease (CVD) (yes or no).

2.6. Statistical analyses

Baseline characteristics according to extreme quartiles of both inflammatory dietary patterns were explored by using the chi-square test for categorical variables and the independent samples *t*-test for continuous variables. The Kruskall Wallis test was applied to test the median (IQR) of the separate food groups according to dietary pattern quartiles because the food groups were not normally distributed. Multivariable linear mixed models fit by restricted maximum likelihood with regression coefficients (B) and 95% CI were used to identify longitudinal associations between the inflammatory dietary patterns and depressive symptoms (continuous CES-D scores). Linear mixed models has the capacity to account for the dependency of repeated measurements obtained from the same individual over time by including a random intercept in the model. Hereby we allowed individuals' repeated measurements (3, 6 and 9 years of follow-up) of the CES-D scores to fluctuate over time. The basic model included random intercepts only, thereafter we added random slopes to the model for covariates that may change over time (marital status, smoking status, physical activity, use of anti-depressants or anti-inflammatory drugs, waist circumference, diabetes and CVD) and tested for sig-

nificant improvement in fit (using likelihood ratio tests ($P < 0.05$)), however, no statistically significant improvements were observed and therefore we used models with random intercepts only. General estimated equations (GEE) logistic regression was used for the analysis of CES-D as binary outcome variable to test longitudinal associations between inflammatory dietary patterns and depression (yes/no). We used an exchangeable correlation structure to take within-subject dependencies into account and we assumed the correlations in this structure between subsequent measurements to be the same, irrespective of the length of the time interval. As mixed models, GEE also takes into account the correlation between repeated observations for the same subject but is better suitable for binary outcomes compared to mixed models. Odds ratios (95% CI) from these models can be interpreted as averaged likelihood of being depressed over time (9 years). In order to check whether the diet-depression relationship was similar for participants with different lifestyles, the interaction between waist circumference and diet, smoking status and diet, CVD and diet and diabetes and diet were tested, but no significant interactions were observed. The first model was adjusted for age, sex, marital status, education and baseline depressive symptoms. In model 2 we additionally adjusted for IADL, smoking status and physical activity. We further adjusted for use of anti-depressants and use of nonsteroidal anti-inflammatory drugs in model 3. Finally we additionally adjusted for co-morbidity (waist circumference, diabetes, CVD). No adjustment was made for alcohol because alcohol was included as a food group in the dietary pattern analysis (wine and other alcoholic beverages). We also did not adjust for energy intake in regression models since the food groups used in RRR were already energy-adjusted.

As sensitivity analyses, we performed RRR with waist circumference-adjusted inflammatory biomarkers as response variables (using the residual method) because waist circumference is likely to be related to inflammation and dietary intake, hereby the response variables might be less prone to confounding by waist circumference in the stage of dietary pattern identification (Schulze et al., xxxx). Moreover, waist circumference has been previously associated with higher inflammatory levels in the current study population (Schrager et al., 1985). Dietary pattern analyses (RRR) were performed with SAS version 9.4 and the remaining analyses were conducted using SPSS version 22.

3. Results

3.1. Study population

We excluded participants with CRP levels $\geq$10 (n = 133) due to possible bias of acute diseases and we excluded participants with missing data on depression (n = 62) or inflammatory biomarkers (n = 133). This left us with 827 participants at baseline for further analyses. Baseline characteristics according to extreme quartiles of inflammatory dietary patterns are presented in table 2. Participants in the highest quartile of inflammatory dietary pattern I were older and less educated than participants in the lowest quartile. Furthermore, participants in quartile 4 were more inactive, smoked less, had higher IADL scores, lower energy intakes and used more anti-depressant medication than participants in quartile 1. Finally, participants in the fourth quartile of dietary pattern I showed higher levels of TNF-α and CRP than participants in the first quartile (Table 2).

When comparing extreme quartiles of inflammatory dietary pattern II, participants in the highest quartile were more often female, were less educated, had higher IADL scores, higher energy intakes, used more anti-inflammatory drugs and had fewer depressive symptoms than participants in the lowest quartile. Finally, participants in the highest quartile had higher levels of IL-18 than participants in the lowest quartile (Table 2).

3.2. Dietary pattern analysis

The food groups and their corresponding factor loadings of the identified dietary patterns that are used for subsequent analyses are presented in Table 3. The first dietary pattern analysis, with CRP, TNF-α and IL-6 as response variables, retained three dietary pattern scores, whereas the second dietary pattern analysis (with CRP, IL-18, IL-1ra and IL-1β as response variables) retained four dietary pattern scores, reflecting the number of included response variables. The first identified dietary patterns in both RRR analyses were used for further analyses due to the highest amount of explained variation in food groups and response variables and were therefore used for subsequent analyses.

Higher scores on the first dietary pattern indicated high intakes of sweet snacks, refined grains, pasta, rice and sauce and low intakes of bread, game, shellfish, other alcoholic beverages, other vegetables, wine, dairy products, olive oil and fish. This dietary pattern was labeled as 'inflammatory dietary pattern I' and was highly correlated to TNF-α (r = 0.80) and CRP (r = 0.60) and was negatively correlated to IL-6 (r = −0.11). In total, the dietary pattern explained 3.7% of the food groups and 1.8% of the response variables (Table 3). For the second dietary pattern, higher scores indicate high intakes of pasta, sugar-sweetened beverages, processed meat, chocolate and sweets, sauce, other alcoholic beverages and low intakes of dairy products, fruit, added sugars, olive oil, butter, fish, coffee and tea and vegetable oil. This dietary pattern was labeled as 'inflammatory dietary pattern II' and was highly correlated to IL-18 (r = 0.81) and to a lower extent to IL-1β, IL-1ra and CRP (r = 0.37, 0.36 and 0.30, respectively) and explained 4.1% of the food groups and 1.4% of the response variables. Overall, the two identified dietary patterns share several similarities, such as the positive correlation with CRP and high intakes of pasta and sauce. This was confirmed by the moderate correlation between the two dietary patterns (r = 0.44). The major difference between the two identified dietary patterns concerning inflammatory markers is the high correlation with TNF-α for inflammatory dietary pattern I and the high correlation with IL-18, IL-1β, IL-1ra for inflammatory dietary pattern II. Additionally, we observed a major difference in the food group "other alcoholic beverages" which was characteristic for inflammatory dietary pattern II but not for inflammatory dietary pattern I.

As additional analysis, we investigated the contribution of the actual intake of the most important food groups across quartiles per dietary pattern. For inflammatory dietary pattern I, the intake of all food groups (in g/d) changed significantly across increasing quartiles of the dietary pattern score, except for sugar-sweetened beverages, processed meat, added sugar and butter of which the was similar across quartiles. For inflammatory dietary pattern II, a significant difference in intake was observed across increasing dietary pattern quartiles in all food groups except for refined grains and shellfish (Supplementary Table 1).

3.3. Longitudinal association between baseline dietary pattern scores and depressive symptoms (continuous score)

The longitudinal association between continuous scores and quartiles of dietary patterns at baseline and depressive symptoms over time are presented in table 4. We did not find a statistically significant association between any of the dietary patterns and depressive symptoms over a period of nine years in any of the models (Table 4).

Table 2
Baseline characteristics of the InCHIANTI participants according to extreme inflammatory dietary pattern quartiles.

Characteristic	Inflammatory dietary pattern I			Inflammatory dietary pattern II		
	Q1	Q4	P value	Q1	Q4	P value
Socio-demographic variables						
Age in years, mean (SD)	72.8 (±5.9)	74.6 (±6.9)	0.004	73.6 (±6.3)	73.9 (±7.2)	0.107
Sex, female, n (%)	109 (52.7%)	117 (56.5%)	0.427	135 (65.2%)	106 (51.5%)	0.007
Marital status, n (%)			0.881			0.146
Never married	16 (7.7%)	17 (8.2%)		10 (4.8%)	21 (10.2%)	
Married	130 (62.8%)	122 (58.9%)		133 (64.3%)	132 (64.1%)	
Widower/divorced	61 (29.5%)	68 (32.9%)		64 (30.9%)	53 (25.7%)	
Education in years, mean (SD)	6.1 (±3.7)	5.2 (±2.8)	0.013	6.1(±3.8)	5.6 (±3.2)	0.007
Behavioral variables						
Smoking status, n (%)			0.013			0.619
Never smoker	108 (52.2%)	128 (61.8%)		128 (61.8%)	110 (53.4%)	
Former smoker	58 (28.0%)	56 (27.1%)		52 (25.1%)	72 (35.0%)	
Current smoker	41 (19.8%)	23 (11.1%)		27 (13.0%)	24 (11.7%)	
IADL, mean (SD)	0.33 (±1.01)	0.75 (±1.73)	0.008	0.37 (±1.11)	0.64 (±1.63)	0.056
Physical activity, n (%)			0.030			0.414
Inactive	26 (12.6%)	47 (22.7%)		32 (15.5%)	42 (20.4%)	
Light	91 (44.0%)	91 (44.0%)		98 (47.3%)	88 (42.7%)	
Moderate to intense	90 (43.5%)	69 (33.3%)		77 (37.2%)	76 (36.9%)	
Waist circumference, mean (SD)	92.0 (±12.9)	91.0 (±10.9)	0.114	91.2 (±11.9)	90.6 (±11.1)	0.454
Energy intake in kcal/d, mean (SD)	2068 (±570)	1994 (±600)	>0.001	1990 (±536)	2004 (±640)	0.019
Health status variables						
MMSE scores, mean (SD)	25.6 (±3.3)	25.1 (±3.1)	0.405	25.7 (±3.0)	25.5 (±3.1)	0.104
CES-D score, mean (SD)	12.6 (±8.3)	13.5 (±9.3)	0.456	13.8 (±9.0)	12.3 (±9.2)	0.249
Use of NSAID, n (%)	16 (7.7%)	18 (8.7%)	0.653	14 (6.8%)	21 (10.2%)	0.025
Use of antidepressants, n (%)	6 (2.9%)	14 (6.8%)	0.036	7 (3.4%)	13 (6.3%)	0.215
Diabetes, n (%)	26 (12.6%)	21 (10.1%)	0.610	20 (9.7%)	26 (12.6%)	0.245
CVD, n (%)	53 (25.6%)	71 (34.3%)	0.273	56 (27.1%)	67 (32.5%)	0.227
Depression, n (%)	45 (21.7%)	54 (26.1%)	0.074	55 (26.6%)	43 (20.9%)	0.044
Inflammatory markers						
IL-6	102.0 (±44.5)	102.3 (±55.6)	0.686	100.8 (±49.1)	96.9 (±48.8)	0.076
TNF-α	2555 (±580)	2896 (±807)	>0.001	2656 (±731)	2746 (±764)	0.102
CRP	2.66 (±2.11)	3.52 (±2.41)	>0.001	2.70 (±2.18)	3.16 (±2.40)	0.242
IL-18	402.9 (±146.1)	415.3 (±171.4)	0.115	372.6 (±143.3)	425.6 (±162.4)	0.001
IL-1ra	133.1 (±70.8)	151.5 (±98.0)	0.139	135.0 (±72.7)	150.7 (±95.3)	0.231
IL-1β	0.30 (±1.21)	0.57 (±2.76)	0.101	0.19 (±0.43)	0.40 (±1.95)	0.575

Table 3
Food groups that were characteristic for dietary patterns I and II using reduced rank regression with their corresponding factor loadings ≥0.20.

Inflammatory dietary pattern I[$]	Load	Inflammatory dietary pattern II[#]	Load
Positive loadings			
Sweet snacks	0.37	Pasta	0.27
Refined grains	0.26	Sugar sweetened beverages	0.24
Pasta	0.24	Processed meat	0.23
Rice	0.24	Chocolate and sweets	0.22
Sauce	0.20	Sauce	0.20
		Other alcoholic beverages	0.20
Negative loadings			
Bread	−0.33	Dairy products	−0.44
Game	−0.31	Fruit	−0.27
Shellfish	−0.25	Added sugar	−0.22
Other alcoholic beverages	−0.25	Olive oil	−0.22
Other vegetables	−0.24	Butter	−0.20
		Fish	−0.20
		Coffee and tea	−0.20
Explained variation:			
Food groups	3.7%		4.1%
Response variables	1.8%		1.4%
Pearson correlation coefficients			
IL-6	−0.11		
TNF-α	0.80		
CRP	0.60		0.30
IL-1β			0.37
IL-1ra			0.36
IL-18			0.81

[$] Dietary pattern I incorporated CRP, IL-6 and TNF-α as response variables
[#] Dietary pattern II incorporated CRP, IL-18, IL-1ra and IL-1β as response variables

3.4. Longitudinal association between dietary pattern scores and depression (using cut-off)

In Table 5, the longitudinal association is presented of continuous scores and quartiles of dietary patterns with depression (CES-D ≥20) over time. When looking at inflammatory dietary pattern I, higher consumption of this dietary pattern (both continuous scores as when comparing extreme quartiles) was not associated with depression over a period of nine years. For inflammatory dietary pattern II, participants from the highest quartile were less likely to be depressed over time compared to those from the lowest quartile. Similar results were found when using continuous dietary pattern scores. Both associations were statistically significant (Table 5).

3.5. Sensitivity analyses

We repeated RRR with waist circumference-adjusted (instead of BMI-adjusted) inflammatory biomarkers as response variables additional to the energy-adjusted food groups. We identified similar dietary patterns as compared to the original dietary pattern analyses (dietary pattern I was characterized by high intakes of refined grains, sweet snacks, sauce, pasta and rice and dietary pattern II was characterized by high intakes of pasta, sauce, soup and other alcoholic beverages). Compared to our main analyses, we observed similar associations between dietary pattern I and depressive symptoms (B = 0.011, 95% CI: −0.02, 0.04, P = 0.506). We did find a stronger negative association between dietary pattern II and depressive symptoms, which was statistically signifi-

Table 4
Prospective association between inflammatory dietary patterns at baseline and continuous depressive symptoms over time.

	Inflammatory dietary pattern I		Inflammatory dietary pattern II	
	B (95% CI)	P value	B (95% CI)	P value
Dietary pattern scores in quartiles				
Model 1				
Q2	0.027 (−0.055, 0.100)	0.522	0.011 (−0.075, 0.100)	0.801
Q3	0.018 (−0.067, 0.102)	0.678	−0.077 (−0.162, 0.009)	0.081
Q4	0.053 (−0.034, 0.140)	0.232	−0.007 (−0.090, 0.078)	0.879
Model 2				
Q2	0.019 (−0.062, 0.101)	0.639	0.004 (−0.080, 0.089)	0.919
Q3	0.017 (−0.066, 0.101)	0.687	−0.078 (−0.163, 0.007)	0.072
Q4	0.041 (−0.045, 0.127)	0.349	−0.022 (−0.106, 0.062)	0.607
Model 3				
Q2	0.025 (−0.056, 0.105)	0.511	0.007 (−0.076, 0.091)	0.862
Q3	0.021 (−0.062, 0.104)	0.624	−0.083 (−0.167, 0.002)	0.055
Q4	0.029 (−0.057, 0.115)	0.507	−0.035 (−0.118, 0.048)	0.411
Model 4				
Q2	0.027 (−0.060, 0.114)	0.547	0.015 (−0.077, 0.107)	0.749
Q3	0.009 (−0.083, 0.102)	0.842	−0.079 (−0.172, 0.014)	0.094
Q4	0.038 (−0.057, 0.133)	0.432	−0.039 (−0.131, 0.052)	0.398
Continuous dietary pattern scores				
Model 1	0.024 (−0.013; 0.061)	0.203	−0.016 (−0.052; 0.020)	0.380
Model 2	0.025 (−0.012; 0.062)	0.184	−0.019 (−0.055; 0.016)	0.288
Model 3	0.022 (−0.015; 0.058)	0.245	−0.025 (−0.061; 0.010)	0.160
Model 4	0.027 (−0.013; 0.066)	0.185	−0.028 (−0.066; 0.010)	0.148

Model 1: adjusted for sex, age, marital status, education in years and continuous CES-D scores at baseline.
Model 2: adjusted for model 1 and for IADL, smoking status, physical activity.
Model 3: adjusted for model 2 and for antidepressant use and anti-inflammatory drugs.
Model 4: adjusted for model 3 and for CVD, diabetes and waist circumference.

Table 5
Prospective association between inflammatory dietary patterns at baseline and depression (using cut-off)* over time using generalized estimated equations.

	Inflammatory dietary pattern I		Inflammatory dietary pattern II	
	OR (95% CI)	P value	OR (95% CI)	P value
Dietary pattern scores in quartiles				
Model 1				
Q2	1.279 (0.835, 1.960)	0.259	0.885 (0.573, 1.367)	0.583
Q3	0.978 (0.629, 1.519)	0.920	0.775 (0.498, 1.206)	0.259
Q4	1.053 (0.692, 1.602)	0.808	0.704 (0.453, 1.095)	0.120
Model 2				
Q2	1.213 (0.784, 1.878)	0.386	0.826 (0.532, 1.283)	0.395
Q3	0.945 (0.607, 1.472)	0.804	0.741 (0.481, 1.142)	0.174
Q4	0.994 (0.648, 1.524)	0.978	0.635 (0.405, 0.995)	0.048
Model 3				
Q2	1.138 (0.710, 1.825)	0.591	0.851 (0.527, 1.373)	0.507
Q3	0.894 (0.539, 1.482)	0.663	0.646 (0.402, 1.038)	0.071
Q4	0.888 (0.551, 1.433)	0.627	0.576 (0.348, 0.954)	0.032
Model 4				
Q2	1.142 (0.713, 1.828)	0.580	0.840 (0.522, 1.350)	0.470
Q3	0.854 (0.513, 1.423)	0.545	0.620 (0.384, 1.001)	0.050
Q4	0.895 (0.554, 1.448)	0.652	0.564 (0.338, 0.940)	0.028
Continuous dietary pattern scores				
Model 1	1.004 (0.842, 1.198)	0.962	0.891 (0.753, 1.054)	0.177
Model 2	0.979 (0.814, 1.176)	0.818	0.865 (0.729, 1.025)	0.095
Model 3	0.964 (0.789, 1.178)	0.723	0.820 (0.684, 0.982)	0.031
Model 4	0.961 (0.785, 1.175)	0.696	0.806 (0.669, 0.970)	0.022

Model 1: adjusted for sex, age, marital status, education in years and depressive symptoms at baseline.
Model 2: adjusted for model 1 and for IADL, smoking status, physical activity.
Model 3: adjusted for model 2 and for antidepressant use and anti-inflammatory drugs.
Model 4: adjusted for model 3 and for CVD, diabetes and waist circumference.
* Depression were defined as CES-D scores ≥20.

cant (B = −0.029, 95% CI: −0.05, −0.00, P = 0.020), whereas no significant association was found in the main analysis.

4. Discussion

In this study we identified two inflammatory dietary patterns of which inflammatory dietary pattern I was characterized by high intakes of sweet snacks, refined grains, pasta, rice and sauce while inflammatory dietary pattern II was characterized by high consumption of pasta, sugar-sweetened beverages, processed meat, chocolate and sweets, sauce and other alcoholic beverages. Both dietary patterns were highly correlated to inflammatory biomarkers that are presumed to be associated with higher depressive symptoms, however, no longitudinal association was found

between higher consumption of either inflammatory dietary pattern and higher depressive symptoms (as continuous measure) in older adults living in Tuscany, Italy. In contrast, and contrary to expectations, a higher consumption of inflammatory dietary pattern II was associated with a lower risk of depression (operationalized as CES-D > 20).

Our findings for inflammatory dietary pattern I corroborate the results of two other prospective studies performed among older adults where no association was found between depression and unhealthy dietary patterns: a pattern high in fast food, sweet snacks, beverages, dairy products, whole grains, coffee, nuts and eggs (Chan et al., 2014) and a pattern high in fruit (juice), vegetables, nuts, grains, pizza, pasta dishes, chocolates and sweets, snacks, processed meat and high-fat dairy (Gougeon et al., 2015). In contrast, four studies observed that higher scores on inflammatory dietary patterns were associated with higher depressive symptoms, however these studies were performed in middle-aged populations (Shivappa et al., 2016; Sanchez-Villegas et al., 2015; Akbaraly et al., 2016; Lucas et al., 2014). A study performed in U.S. women, that also applied RRR (with CRP, IL-6 and TNF-α as response variables), found that higher scores on an inflammatory dietary pattern consisting of sugar-sweetened beverages, refined grains, red meat, diet soft drinks, margarine, other vegetables and fish was associated with higher depressive symptoms (Lucas et al., 2014). The larger and more heterogeneous study population (n = 43,685 women, aged 50–77 years) with a wide variety in dietary intakes may explain the different findings compared to our study. Furthermore, three studies that applied the a priori DII, observed statistically significant positive associations between higher DII scores and higher incident depressive symptoms (Shivappa et al., 2016; Sanchez-Villegas et al., 2015; Akbaraly et al., 2016). Again, the younger and more heterogeneous populations and the a priori nature of these studies might explain the different observed associations compared to our study.

One possible explanation for the observed null findings in the current study could be insufficient variation in dietary intake between the subjects in our cohort. The lack of variation makes it difficult to study the difference between high and low food intakes. This was confirmed by additional analyses in which we investigated the intake of the most important food groups across dietary pattern quartiles. Even though statistically significant differences were observed in most of the food groups, differences in intake were quite small in some of the groups and may not be practically relevant (e.g. the chocolate and sweets median intake was 2 g/d in quartile 1 versus 4 g/d in quartile 4 of 'inflammatory dietary pattern I'), whereas, the intake of the most important food groups in the U.S. study, a larger variation in intake was observed (Lucas et al., 2014). For example, when comparing the intake of sugar-sweetened beverages, a difference of 80 g/d was observed between Q1 and Q4 of the inflammatory dietary pattern in the U. S. study, whereas in our study no difference (0 g/d) was observed between Q1 vs Q4. For refined grains, a difference of 100 g/d was observed in the U.S. study compared to a difference of 15 g/d in our study. A previous study, performed in the current population, found a protective association between a healthy dietary pattern typically consumed by the Tuscan population and depressive symptoms (Vermeulen et al., 2016). In that study, we included participants below the age of 65 years (n = 298), where more heterogeneity was present for dietary intake. Furthermore, when we stratified by age, the association between the dietary pattern and depressive symptoms was stronger in the participants below 65 years compared to the participants above the age of 65 years (Vermeulen et al., 2016). However, in the current study we were particularly interested in older adults due to the higher inflammatory levels and higher depression incidence in this particular age group.

The observed inverse association between inflammatory dietary pattern II and depression was not in accordance with our expectations as a previous study, performed in the same population, found that higher levels of the inflammatory biomarkers that we used as response variables (IL-18, IL-1ra, IL-1β and CRP) were associated with higher depressive symptoms, of which the association between IL-1ra and depressive symptoms was statistically significant (Milaneschi et al., 2009). As all inflammatory markers were positively correlated with the identified dietary pattern with foods that are considered as unhealthy (sugar-sweetened beverages, processed meat, chocolate and sweets and other alcoholic beverages), we expected that higher consumption of this dietary pattern would be associated with higher depression prevalence. However, the explained variation in the food groups (4.1%) and response variables (1.4%) of inflammatory dietary pattern II is quite low. One might argue whether these dietary patterns optimally represent the included biomarkers. Although, a low amount of explained variation is not uncommon when using biomarkers as response variables, two other studies that performed RRR with biomarkers as response variables, observed an explained variation of 3.9% (Frank et al., 2015) and 4.3% (Heidemann et al., 2005) in the response variables. Another possible explanation for these unexpected findings could be that we used the abovementioned biomarkers as underlying markers for deriving dietary patterns and we did not directly, in contrast to Milaneschi et al., relate the biomarkers to depressive symptoms in the current study. In contrast to the findings of Milaneschi et al., Luciano et al. did not find an association between depressive symptoms and change in inflammation markers in older adults (Luciano et al., 2012). Additionally, a possible explanation for the observed inverse association could be the influence of moderate alcohol intake. Previous studies suggest that moderate alcohol intake in older adults is associated with fewer depressive symptoms compared to abstinence of alcohol (Paulson et al., 2017; Lang et al., 2007). Furthermore, several studies have reported that moderate alcohol consumption lowers CRP levels (Albert et al., 2003) and CRP and IL-6 levels (Volpato et al., 2004) in older adults compared to heavy and non-drinkers. As the food group "other alcoholic beverages" is characteristic for inflammatory dietary pattern II and not for inflammatory dietary pattern I, alcohol intake may attenuate an initial positive association between inflammatory dietary pattern II and depression. Finally, total energy intake may play an important role. When stratifying for depression (yes/no), a significant lower mean energy intake is observed in subjects with depression (1782 kcal) compared to subjects without depression (1976 kcal) (P = >0.001). From this result we can infer that in this specific population, consuming a sufficient amount of energy is an important aspect in addition to the quality of the dietary pattern. This corroborates with a previous study performed by Gougeon et al. who concluded that older adults that eat less, possibly reflecting declining health, are at higher risk of becoming depressed (Gougeon et al., 2015).

Another possible explanation for our null findings could be the moderating effect of waist circumference on inflammation and dietary intake. A higher waist circumference may reflect differences in lifestyle, including dietary patterns, and thus the diet-depression relationship might differ as a result. To examine the moderation effect of waist circumference, we added interaction terms (depression*diet*time) in our regression models, but these appeared not to be statistically significant. Furthermore, we observed no major differences in the diet-depression relationship when incorporating waist circumference-adjusted inflammatory biomarkers as response variables in our RRR-analyses.

To our knowledge, this is the first study that investigated inflammatory dietary patterns in relation to depressive symptoms in older adults. This age group may be of particular interest for this topic since older adults are more susceptible for inflammation as

well as for depressive symptoms compared to younger adults, and dietary improvements might have the potential to reduce both these risks. Another strength of this study is that information on depression was available at four time points, which allowed us to investigate the association longitudinally. Furthermore, we included a validated cut-off point for depression as well as continuous scores for defining depressive symptoms. By investigating continuous scores as well, we take into account methodological issues such as loss of power and continuous scores are more likely to reflect reality as the use of a cut-off point could be considered arbitrary. Finally, using RRR to identify inflammatory dietary patterns is a strength because RRR allows us to incorporate predefined inflammation biomarkers which have been indicated to be closely related to depressive symptoms in previous research. A limitation of the study is that the sample size was fairly small, especially during follow-up (at baseline we included 827 participants, whereas data were available for 356 participants at follow-up 3, which was mainly due to mortality). Another limitation is the questionnaires used for measuring depressive symptoms and dietary intake, which rely on memory. However, additional analyses revealed that no differences were observed in any of the associations under study after adjustment for mini-mental state examination scores. Finally, reverse causation may be present due to the epidemiological design of the study. However, we attempted to minimize bias by adjusting for baseline depressive symptoms in all analyses.

In conclusion, no longitudinal association was observed between the level of consumption of two inflammatory dietary patterns and depressive symptoms in an older Italian population, even though both dietary patterns were positively correlated to inflammatory markers presumed to be associated with higher depressive symptoms. More large-scale longitudinal studies are needed that examine the role of inflammatory dietary patterns in relation to depression in older adults.

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Conflict of interest disclosures

The analyses of the present study were entirely independent, with no industry association. None of the authors had a conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbi.2017.09.005.

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